TG

TG Therapeutics

2018 ECTRIMS Data Review Call

October 2018

TG Therapeutics

Michael S. Weiss, CEO

Forward Looking Safe Harbor Statement

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Overview

Umbralisib (TGR-1202)	Ublituximab (TG-1101)
Next Generation PI3K delta inhibitor	Next Generation anti-CD20 monoclonal antibody
Overcomes 1st generation Toxicity	Glycoengineered for enhanced potency over 1st generation
Activity across NHL and CLL	Activity in Rituxan refractory patients
Once daily oral dosing vs. BID	Shorter infusions than all other anti-CD20s (1.5 v 3-4 hours)

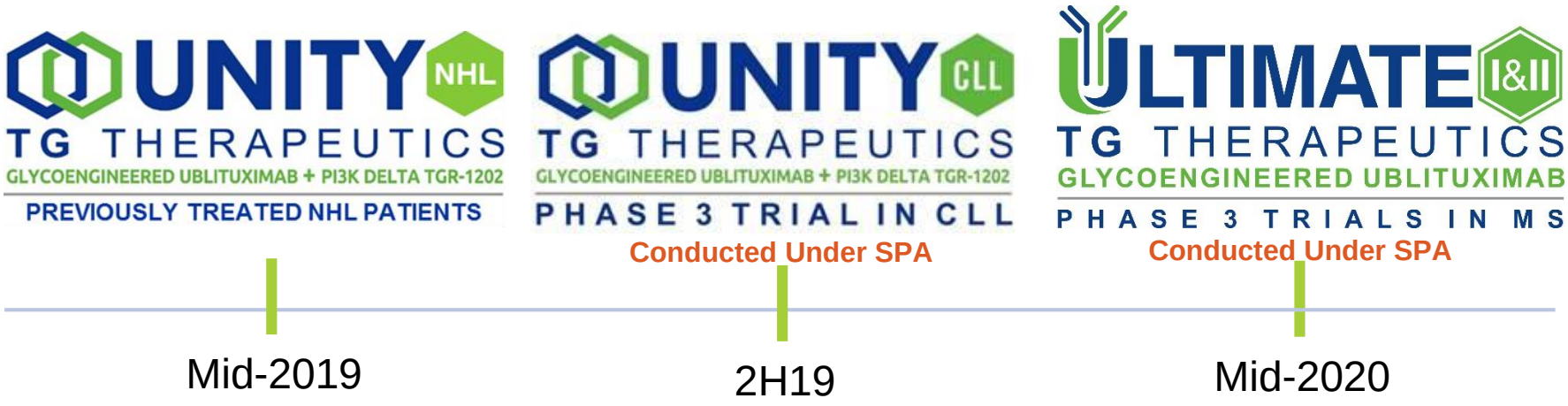
TG At-A-Glance

5 – Pivotal Programs

3 – Diseases (CLL, NHL and MS)

1 – Goal (Bring Novel Medicines to Patients)

All fully enrolled, waiting for data



Final Results of a Placebo Controlled, Phase 2 Multicenter Study of Ublituximab (UTX), a Novel Glycoengineered Anti-CD20 Monoclonal Antibody (mAb), in Patients with Relapsing Forms of Multiple Sclerosis (RMS)

Edward Fox, MD, PhD

Director, MS Clinic of Central Texas

Central Texas Neurology Consultants, PA

Clinical Associate Professor, University of Texas Dell Medical School

Edward Fox, MD, PhD; Amy E. Lovett-Racke, PhD; Matthew Gormley; Yue Liu, MS; Maria Petracca, MD; Matilde Inglese, MD; Richard Shubin, MD; Sibyl Wray, MD; Michael S. Weiss; Jenna A. Bosco; Sean A. Power; Koby Mok, PhD; James Eubanks, PhD

Presented at the Annual Congress of ECTRIMS, October 11, 2018, Berlin, Germany

Disclosures

Research Support:

- TG Therapeutics
- Acorda
- Biogen
- Celgene
- Chugai
- EMD Serono
- MedDay
- Novartis
- Roche-Genentech
- Sanofi Genzyme
- Teva Neuroscience

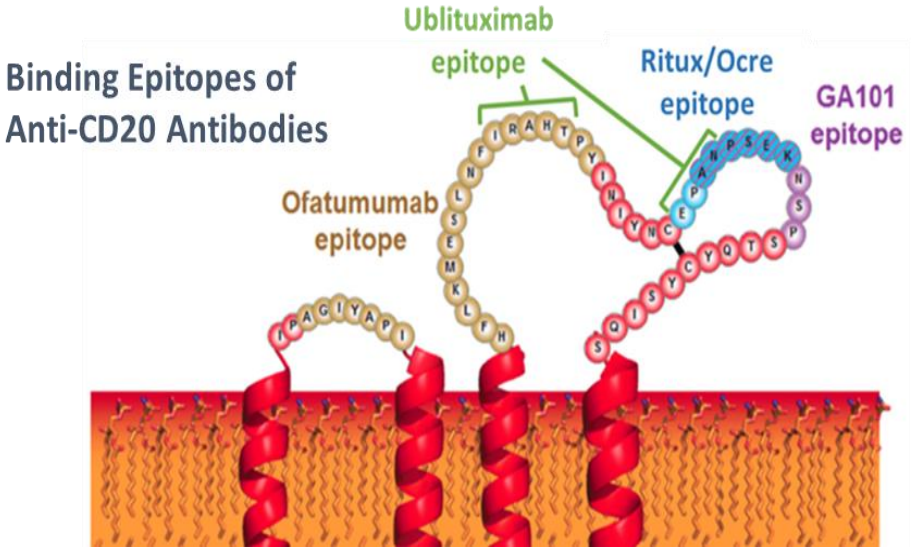
Consultancy/Advisory/Speaker:

- TG Therapeutics
- Acorda
- Bayer
- Biogen
- EMD Serono
- Genentech
- Novartis
- Roche-Genentech
- Sanofi Genzyme
- Teva Neuroscience

Presented analyses included data that were not source document verified.

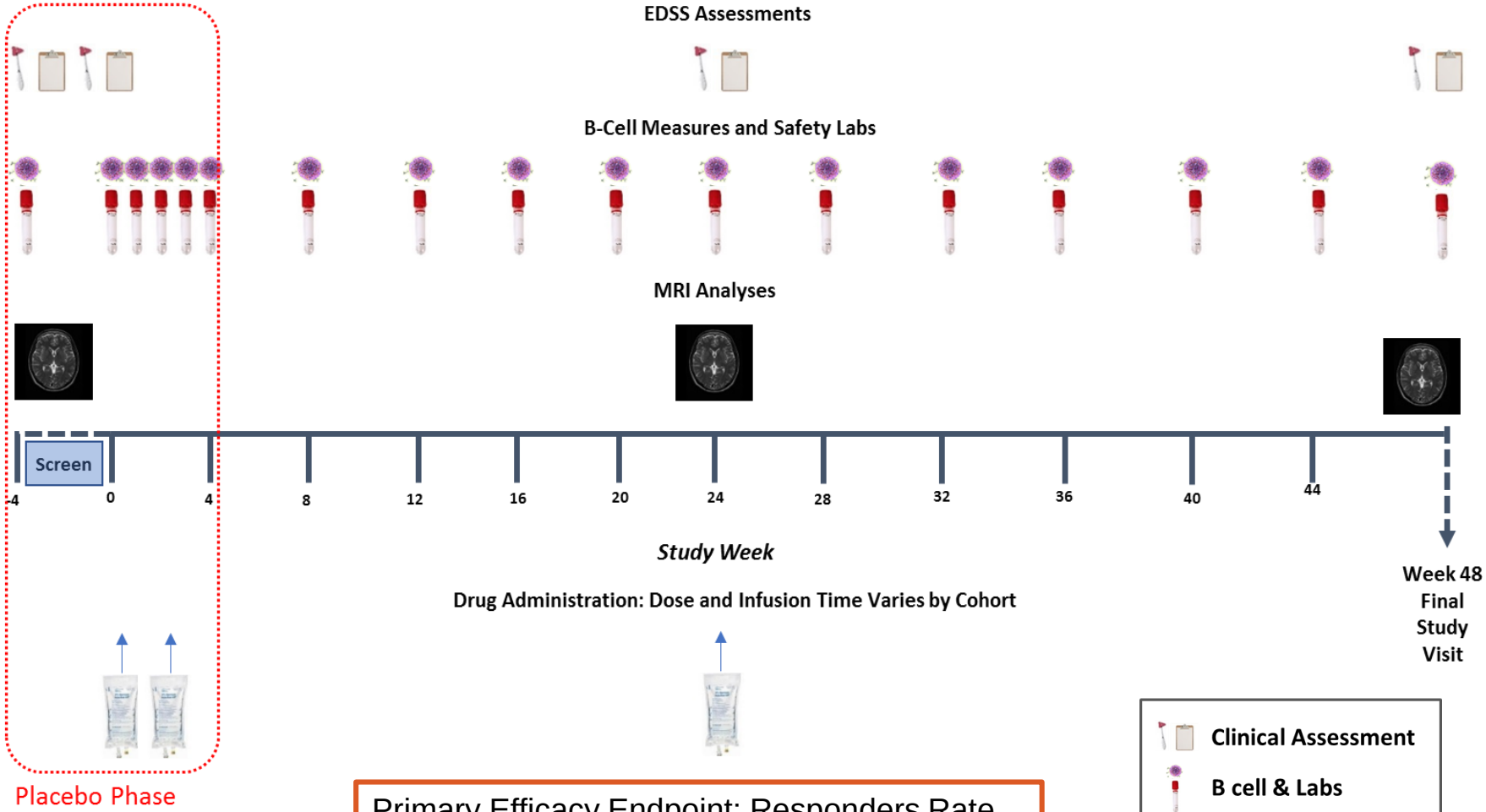
Ublituximab (TG-1101)

- Novel Glycoengineered Anti-CD20 mAb
- Unique protein sequence
- Type 1 Chimeric IgG1 mAb
- Potential advantages over current standard of care:
  - Glycoengineered for significantly enhanced ADCC
  - Activity in “low” CD20 expressing cell lines, a characteristic of rituximab resistance
  - Binds to a novel epitope on CD20
  - Infusion times as low as one hour



Source: Adapted from Ruuls et al 2008

Ublituximab Phase 2 RMS: Design



Primary Efficacy Endpoint: Responders Rate

Responders Rate = Subjects who have ≥95% B-cell depletion at Week 4

Ublituximab Phase 2 RMS: Key Inclusion and Exclusion Criteria

Key Inclusion Criteria:

- 18-55 age
- Diagnosis of RMS (McDonald criteria 2010)
- ≥ 2 relapses in prior 2 years or 1 relapse in the year prior to screening and/or ≥1 Gd enhancing lesion
- Active disease
- EDSS 0-5.5 (inclusive)

Key Exclusion Criteria:

- Treatment with Anti-CD20 within last 12 months
- Treatment with alemtuzumab within last 12 months
- Prior DMT exposure within days of screening
  - 90 days with fingolimod and natalizumab
  - 30 days with glatiramer acetate, interferons, dimethyl fumarate, or glucocorticoids

Ublituximab Phase 2 RMS: Treatment Regimen

	Randomization	Treatment Period		
Cohort	Treatment	Day 1/ Infusion Time	Day 15/ Infusion Time	Week 24/ Infusion Time
1	Placebo (n=2)	Placebo / 4h	Placebo / 3h	-
	UTX (n=6)	150 mg / 4h	450 mg / 3h	450 mg / 1.5h
2	Placebo (n=2)	Placebo / 4h	Placebo / 1.5h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1.5h	450 mg / 1h
3	Placebo (n=2)	Placebo / 4h	Placebo / 1h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1h	600 mg / 1h
4	Placebo (n=2)	Placebo / 3h	Placebo / 1h	-
	UTX (n=6)	150 mg / 3h	600 mg / 1h	600 mg/ 1h
5	Placebo (n=2)	Placebo / 2h	Placebo / 1h	-
	UTX (n=6)	150 mg / 2h	600 mg / 1h	600 mg/ 1h
6	Placebo (n=2)	Placebo / 1h	Placebo/ 1h	-
	UTX (n=6)	150 mg / 1h	600 mg / 1h	600 mg/ 1h

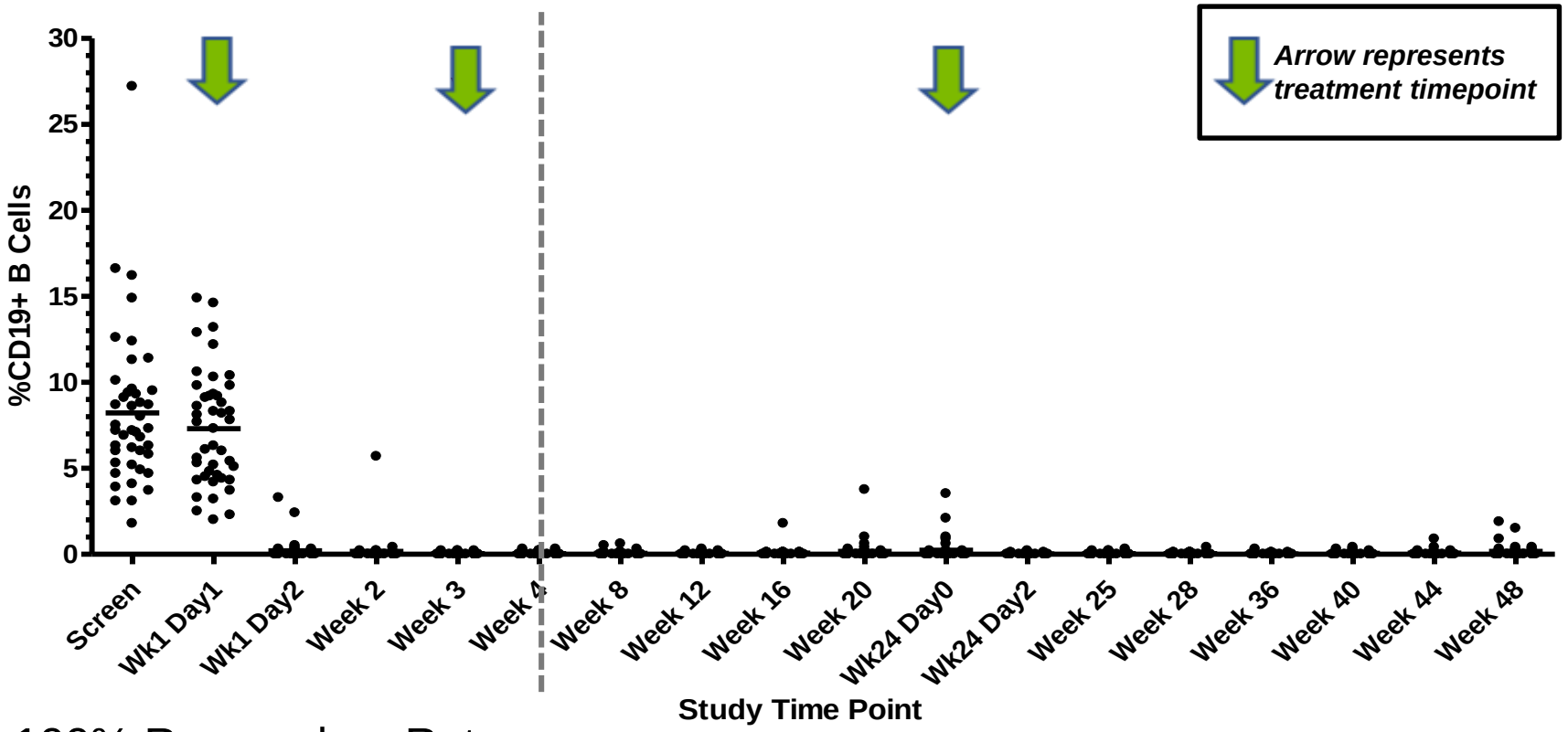
Ublituximab Phase 2 RMS: Baseline Characteristics

Baseline Demographics				
Cohort	Subjects and treatment	Age (Years)[1]	Gender (% Female)	Disease Duration (Years)[1,2]
1	Placebo (n=2)	39±14	50%	15.5±20.4
	UTX (n=6)	43±12	67%	7.1±7.3
2	Placebo (n=2)	44±1	0%	0.9±1.2
	UTX (n=6)	33±10	100%	5.3±7.0
3	Placebo (n=2)	38±7	50%	11.5±7.5
	UTX (n=6)	40±11	67%	13.4±10.0
4	Placebo (n=2)	31±1	67%	0.2±0.1
	UTX (n=6)	39±12	50%	4.4±5.4
5	Placebo (n=2)	36±12	100%	15.4±9.6
	UTX (n=6)	46±1	100%	6.3±5.6
6	Placebo (n=2)	28±1	50%	5.7±2.5
	UTX (n=6)	40±8	33%	8.5±8.4
Total	N=48	40±10	65%	7.7±8.1

[1] **Mean ± Standard Deviation**

[2] **Distribution of time from diagnosis: 22 subjects (46%) were less than 5 years, 10 (21%) were 5-10 years, and 16 (33%) were greater than 10 years**

Ublituximab Phase 2 Results: Primary Endpoint – B cell Depletion



- 100% Responders Rate
  - (48/48) subjects met the primary end point of >95% B-cell depletion from baseline to Week 4, $p<0.001$
- At Week 4, median 99% B cell depletion was observed and maintained at Week 24 and Week 48

Ublituximab Phase 2 RMS: Safety & Tolerability

Adverse Event Summary*

	Regardless of Causality n (%)	Related to Ublituximab n (%)
Patients with an Adverse Event (AE)	48 (100%)	12 (25%)
Patients with a Serious Adverse Event (SAE)	8 (17%)	1 (2%)
AEs leading to Withdrawal	1 (2%)	0 (0%)

**Excludes Infusion Related Reactions (IRRs)*

- **Ublituximab was well tolerated and no drug related discontinuations occurred**
  - One Grade 3 SAE of fatigue was deemed possibly related to ublituximab
  - No deaths reported on study
  - One subject withdrew from the study due to pregnancy but continued to be followed with safety lab monitoring and immunological analyses

Ublituximab Phase 2 RMS: Safety & Tolerability

Adverse Events (AEs) Related to Ublituximab

Event, n (%)	(N=48)	
Most frequently reported adverse events	All Grades	Grade 3/4
Infusion Related Reaction	23 (48%)	- (-)
Headache	4 (8%)	- (-)
Dry Throat	1 (2%)	- (-)
Ear Infection	1 (2%)	- (-)
Ecchymosis	1 (2%)	- (-)
Fatigue	1 (2%)	1 (2%)
Influenza	1 (2%)	- (-)
Neutropenia	1 (2%)	- (-)
Oral Herpes	1 (2%)	- (-)
Pain	1 (2%)	- (-)
Rash	1 (2%)	- (-)
Staphylococcal Infection	1 (2%)	- (-)
Throat Irritation	1 (2%)	- (-)

- Most common Adverse Event (AE) was infusion-related reactions
- No Grade 3/4 Infusion Related Reactions (IRRs)

Ublituximab Phase 2 RMS: Infusion Related Reaction (IRR)

All IRRs Related to Ublituximab

	Ublituximab Infusions			Total Patients with ≥1 IRRs
	Day 1 (n=48)	Day 15 (n=48)	Week 24 (n=46)	
Total IRRs by Day	21 (44%)	5 (10%)	7 (15%)	23 (48%)

Day 1 Infusion Time	n	Day 1 IRRs
4 hours	**24**	7 (33%)
≤3 hours	**24**	14 (58%)

ULTIMATE Phase 3 Dose

- IRRs were most frequent with the first infusion (Day1)
- Day 1 dose infused in ≤3 hours resulted in higher rates of IRRs
- IRRs were infrequent on Day 15 and Week 24 and did not appear to increase with higher doses or faster infusion times
- 77% of total infusions did not result in an IRR

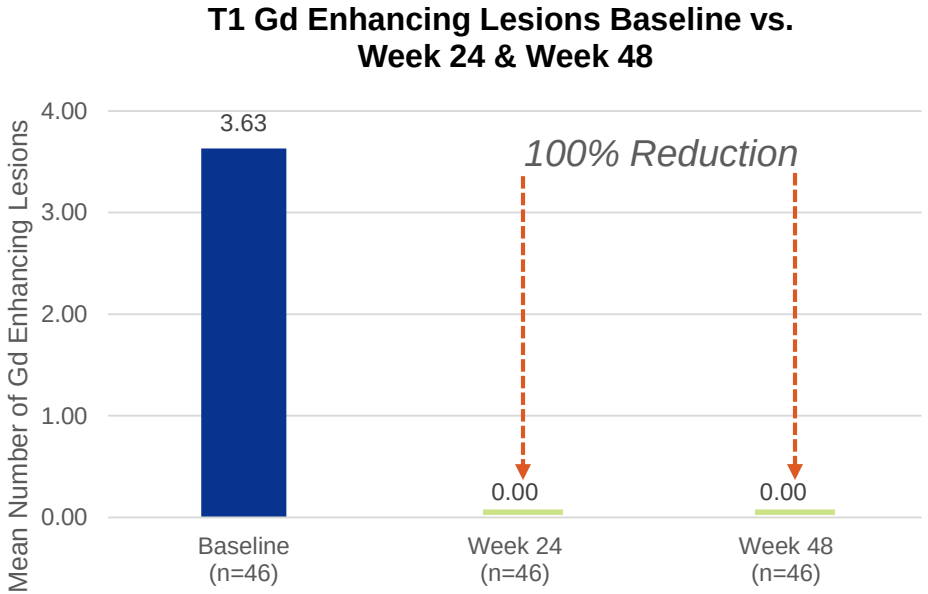
Ublituximab Phase 2 RMS: MRI T1 Gd Enhancing Lesions

Baseline (n=46):

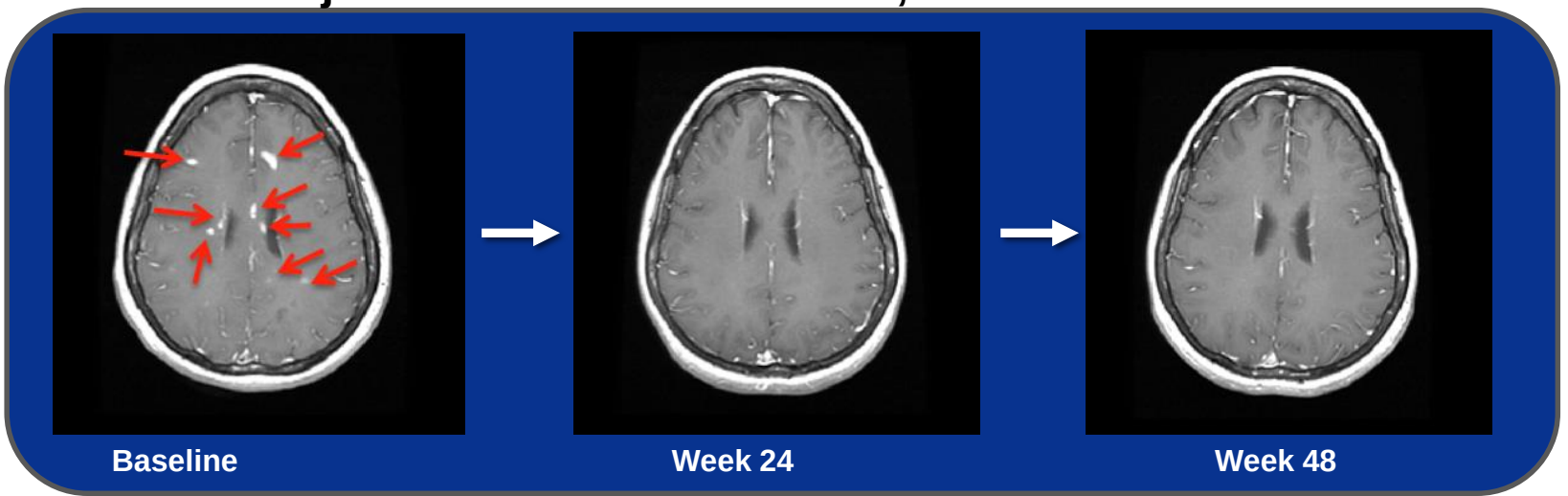
- Mean = 3.63 ± 7.80 T1 Gd lesions
- 39% had ≥ 1 T1 Gd lesions
- 26% had ≥ 4 T1 Gd lesions

Week 24 & Week 48 (n=46):

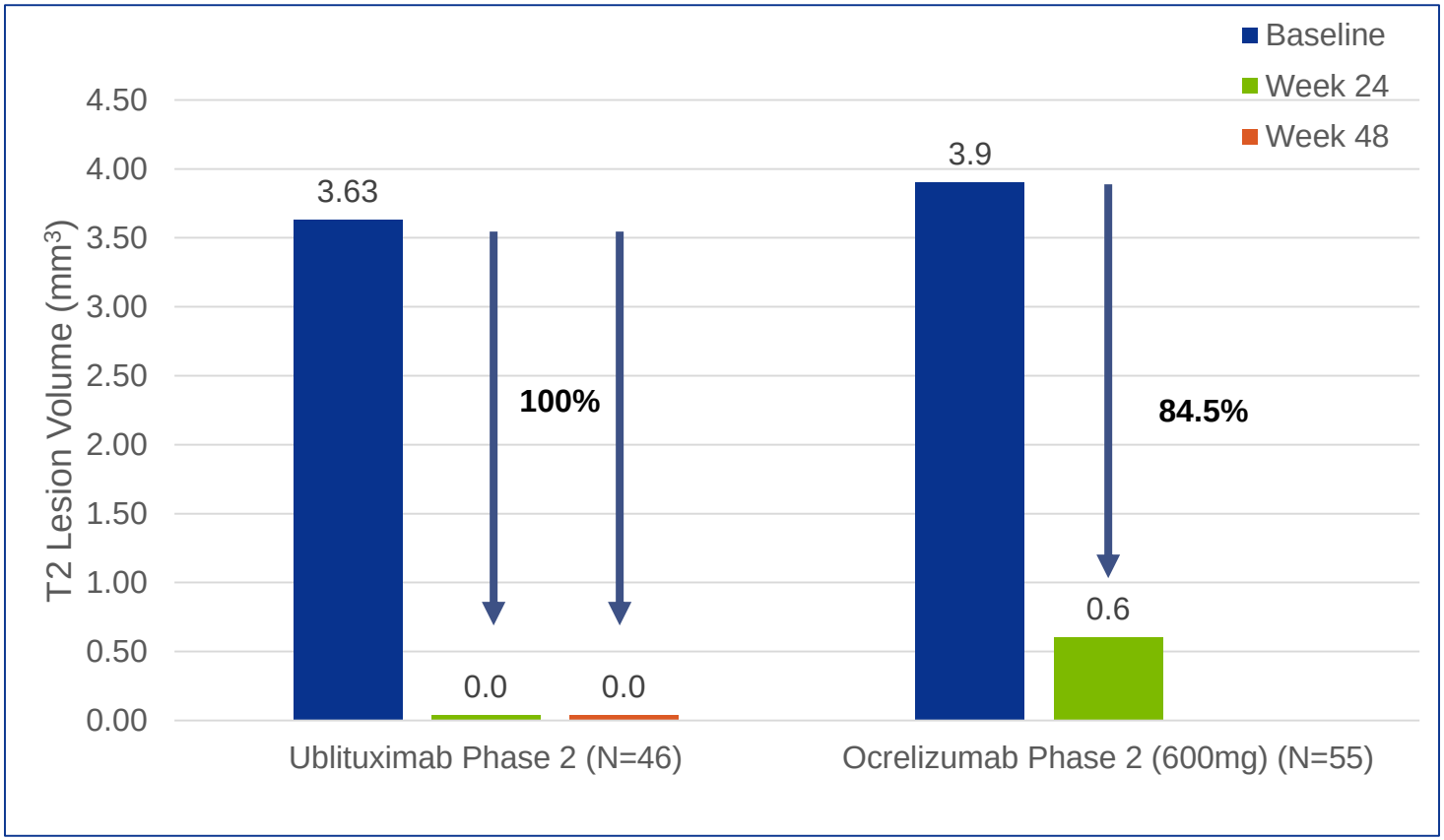
- No T1 Gd lesions found in any scans
- 100% reduction from baseline *(p=0.003)*



Subject T1 Gd MRI at Baseline, Week 24 & Week 48



Gd-Enhancing Lesions

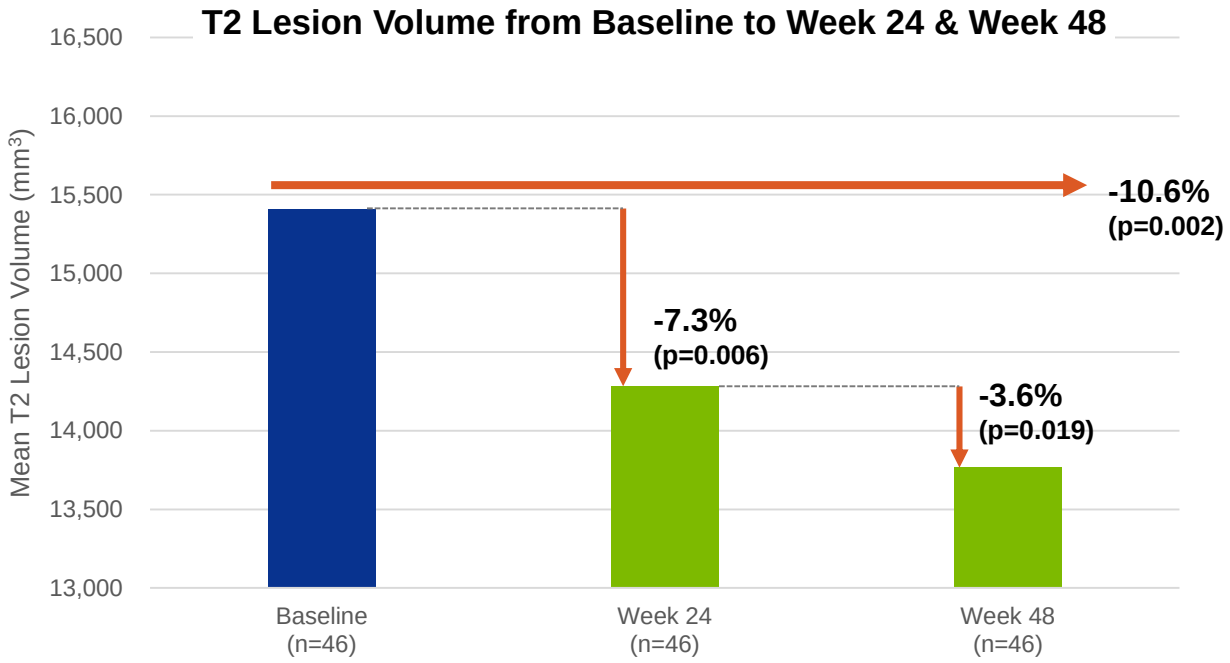


Note: Pooled Opera I& II Phase 3 Ocrelizumab Trials:

- 94% reduction in Gd enhancing lesions when compared to Rebif at Week 96

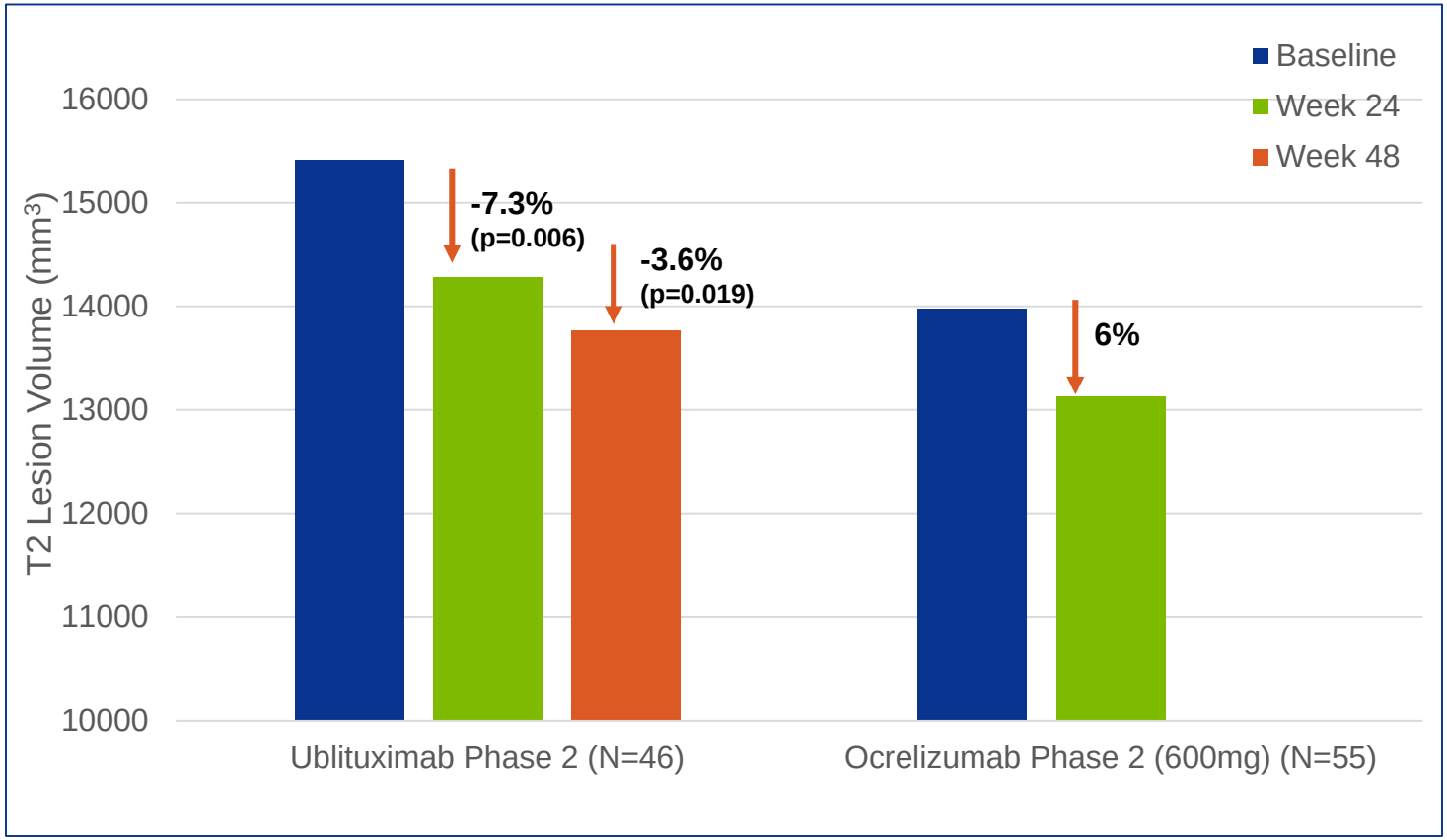
Fox E et al., Presented at ECTRIMS Annual Meeting 2018
Kappos L et al. Lancet. 2011; 378:1779-1787
Hauser SL et al. NEJM. 2017; 376:221-234

Ublituximab Phase 2 RMS Results: MRI T2 Lesion Volume



- Decrease of 7.3% in T2 lesion volume at Week 24 compared to baseline and a further decrease of 3.63% from Week 24 to Week 48
- The mean number of new/enlarging (NEL) T2 lesions from baseline to Week 24 was 0.20 ± 0.43 NEL/subject
- The mean number of new/enlarging (NEL) T2 lesions from Week 24 to Week 48 was 0.04 ± 0.29 NEL/subject

T2 Lesion Volume



Fox E et al., Presented at ECTRIMS Annual Meeting 2018
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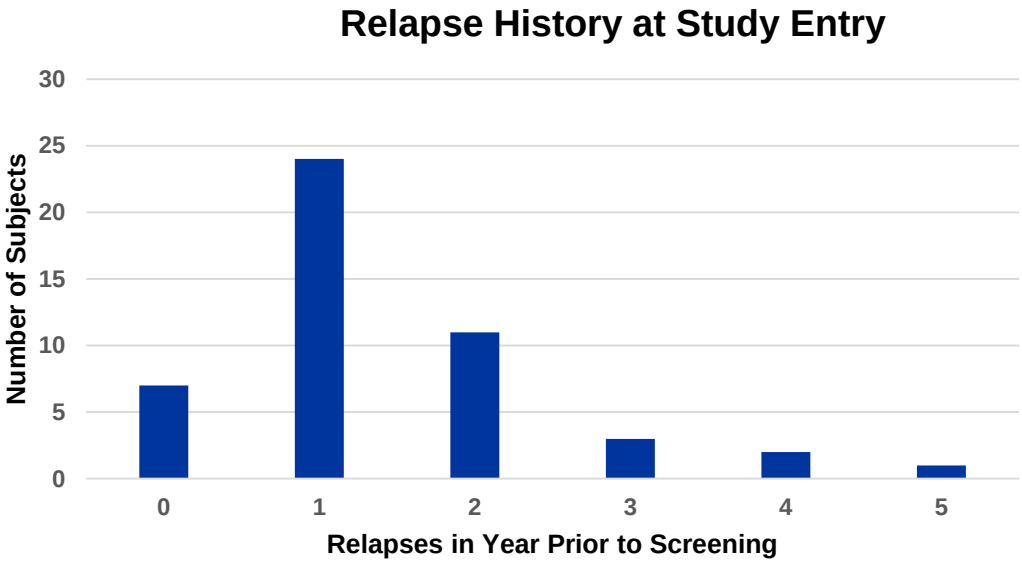
Ublituximab Phase 2 RMS Results: Annualized Relapse Rate (ARR)



- 86% of subjects experienced ≥1 relapse in the year prior to screening
- Mean number of relapses = 1.45
  Median = 2

At Week 48:

- Annualized Relapse Rate (ARR) of 0.07
  - ARR calculated based on 48 subjects with a mean follow up of approximately 47 weeks (20 min – 48 max weeks)
- 93% of subjects were relapse free

Ublituximab Phase 2 RMS Results: Disability

- Mean EDSS at baseline was 2.44 ± 1.36; Median=2.5 (n=48)
- Disability at Week 48:
  - 7% of subjects met criteria for 24 Week Confirmed Disability Progression (CDP)
  - 17% of subjects met criteria for 24 Week Confirmed Disability Improvement (CDI)

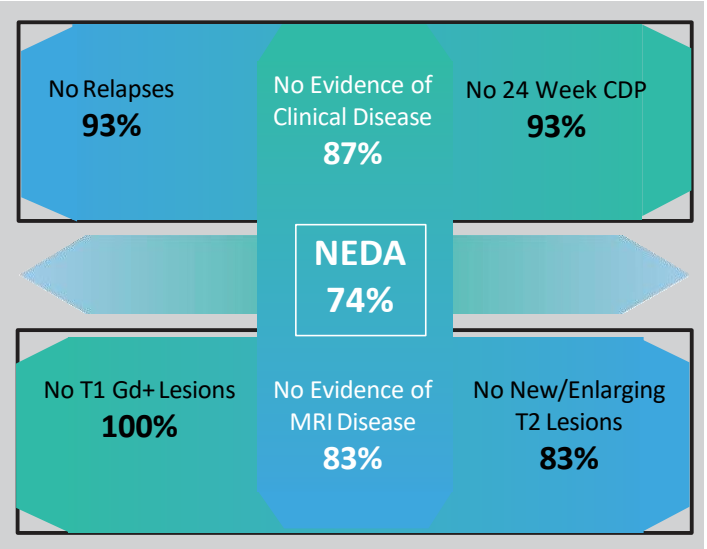
Disability & Relapse

Disability Endpoint	Ublituximab Phase 2 (N=46) (Week 48)	Ocrelizumab Phase 2 (N=55) (24 Weeks)	Opera I&II (N=827) (96 Weeks)
No Confirmed Disability Progression (CDP)	93%	N/A	90.6% (Opera I) 86.8% (Opera II)
Confirmed Disability Improvement (CDI)	17%	N/A	20.7%
% Relapse Free	93%	87%	80%
ARR	0.07	0.13	0.156

Fox E et al., Presented at ECTRIMS Annual Meeting 2018
Kappos L et al. Lancet. 2011; 378:1779-1787
Hauser SL et al. NEJM. 2017; 376:221-234

Ublituximab Phase 2 RMS Results: NEDA at Week 48

- At Week 48, 46* subjects received all assessments to be evaluated for NEDA:
  - 93% of subjects were relapse free
  - 93% of subjects did not experience 24 week confirmed disability progression (CDP)
  - 100% of subjects did not have any Gd enhancing lesions
  - 83% of subjects did not have any new/enlarging T2 lesions on any scan (either Week 24 or Week 48)
  - 74% of subjects achieved clinical and MRI outcomes consistent with NEDA



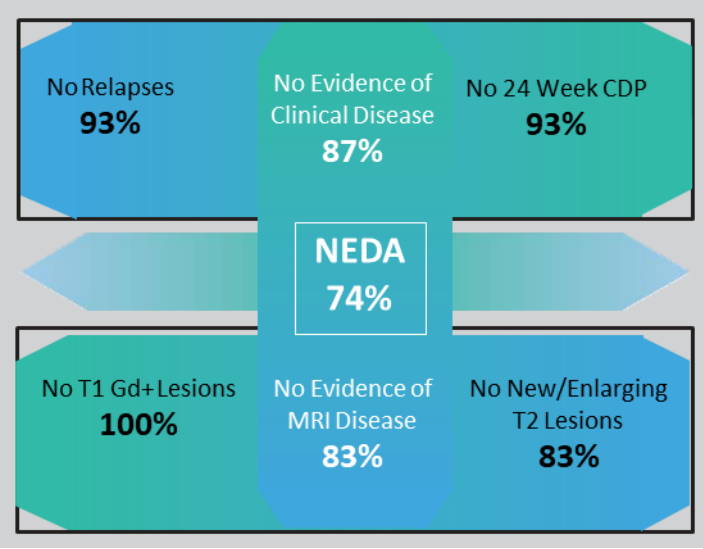
** 2 of the total 48 patients did not have Week 24 MRI or EDSS assessments therefore only 46 patients had received all assessments to be evaluated for NEDA*

24 Week Confirmed Disability Progression (CDP) is defined as an increase of ≥ 1.0 point from the baseline EDSS score (that is not attributable to another etiology e.g. fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥ 0.5 when the baseline score is above 5.5, that is confirmed in a subsequent EDSS assessment 24 weeks later

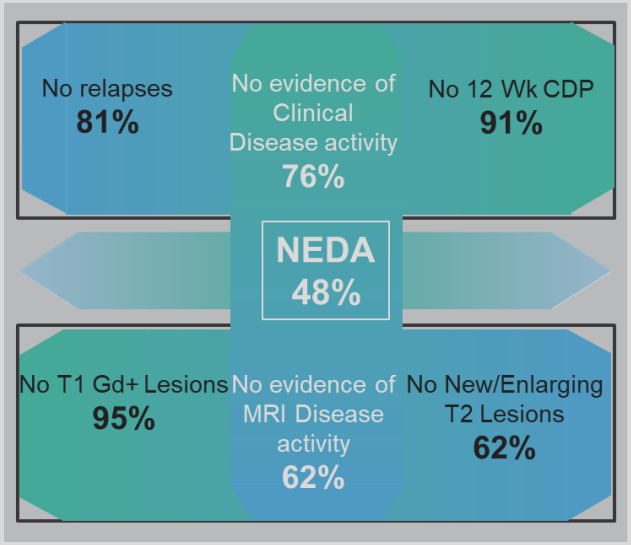
NEDA is defined as subjects without relapses, MRI activities (no T1 Gd+ lesions and no new/enlarging T2 lesions), and no 24-week confirmed disability progression

NEDA: Ublituximab Phase 2 & OPERA I & II

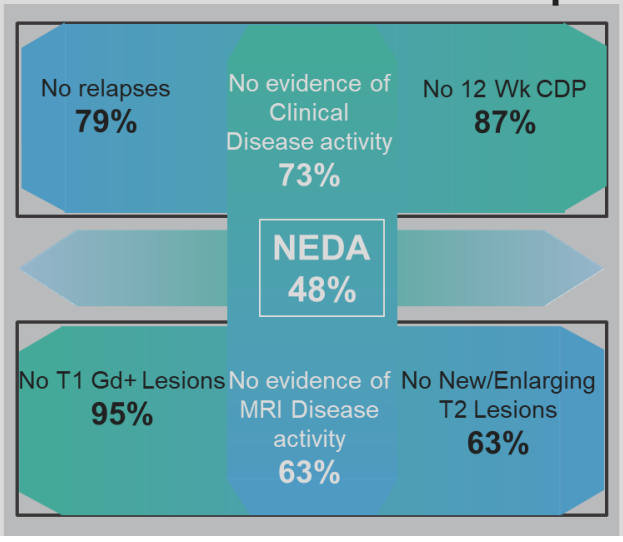
Ublituximab at Week 48



Ocrelizumab at Week 96 – Opera I



Ocrelizumab at Week 96 – Opera II



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Kappos L et al. Lancet. 2011; 378:1779-1787
Hauser SL et al. NEJM. 2017; 376:221-234

Ublituximab Phase 2 RMS: Conclusions

- B cells are efficiently depleted in most patients within 24 hours of receiving the first dose of ublituximab
  - Median 99% B cell depletion was observed at Week 4, and maintained at Week 24 and Week 48
- Ublituximab was well tolerated and the most frequent AEs (all Grade 1 or 2) were Infusion Related Reactions (IRRs)
- No study discontinuations related to ublituximab

Ublituximab Phase 2 RMS: Efficacy Conclusions

At Study Conclusion (Week 48 of Ublituximab Treatment):

- Annualized Relapse Rate (ARR) of 0.07
- 93% of subjects were relapse free
- No T1 Gd enhancing lesions were detected in any subjects at Week 24 or at Week 48
- 74% of subjects fulfilled the criteria for NEDA

A rapid infusion time, as low as one hour, of 450mg ublituximab was well tolerated, produced high levels of B cell depletion and is now being studied in the Phase 3 ULTIMATE trials

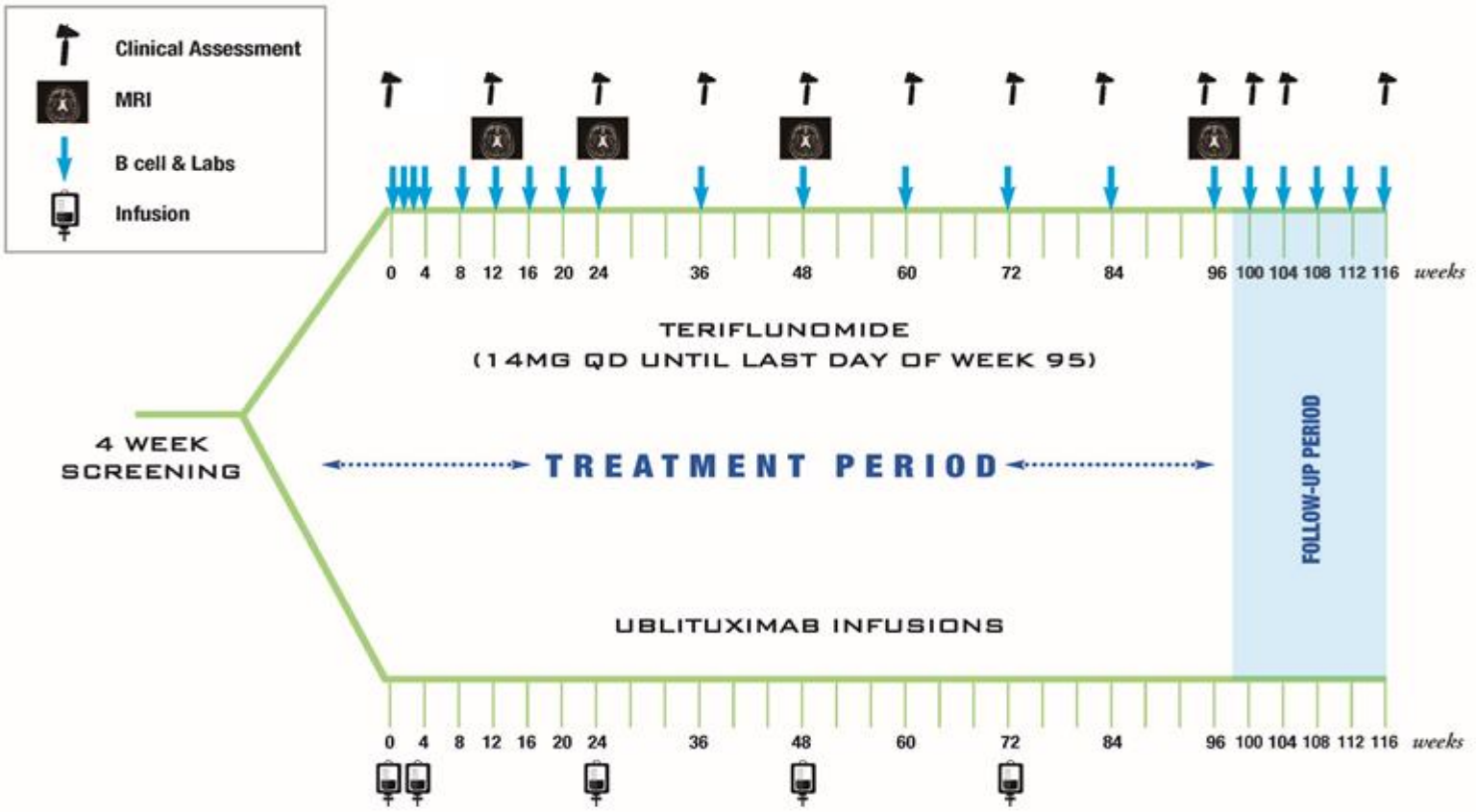
Ublituximab (TG-1101)
Phase 3
ULTIMATE I & II Trials

Edward Fox, MD, PhD

ULTIMATE I and II Study Design

- ULTIMATE I and II are two independently conducted Phase 3 registration trials for ublituximab in relapsing MS
- Identical in design and balanced with respect to location of study sites
- Randomized, Double-Blind, Double-Dummy, Active Comparator
  - Patients randomized 1:1 to ublituximab plus oral placebo or teriflunomide plus IV placebo

ULTIMATE I and II Study Design



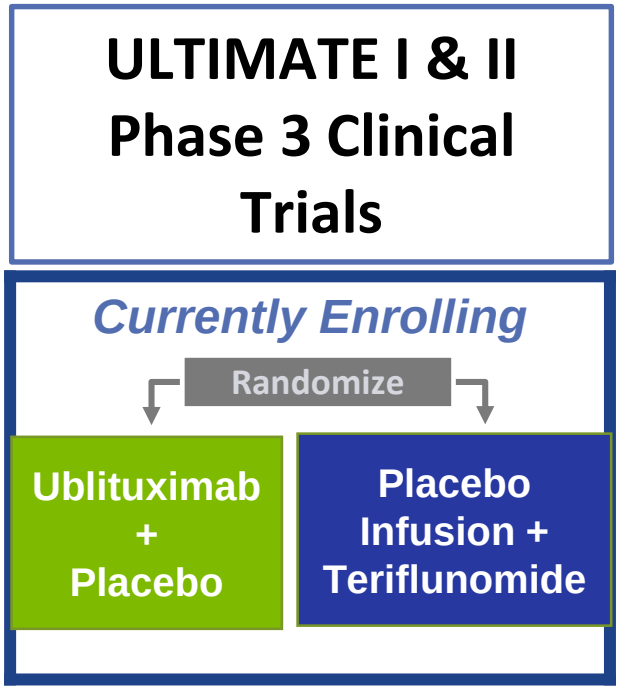
- **Primary Endpoint:** Annualized Relapse Rate (ARR) at 96 weeks in RMS subjects treated with ublituximab
- **Enrollment complete in the ULTIMATE Phase 3 Program**

TG Therapeutics

Michael S. Weiss, CEO

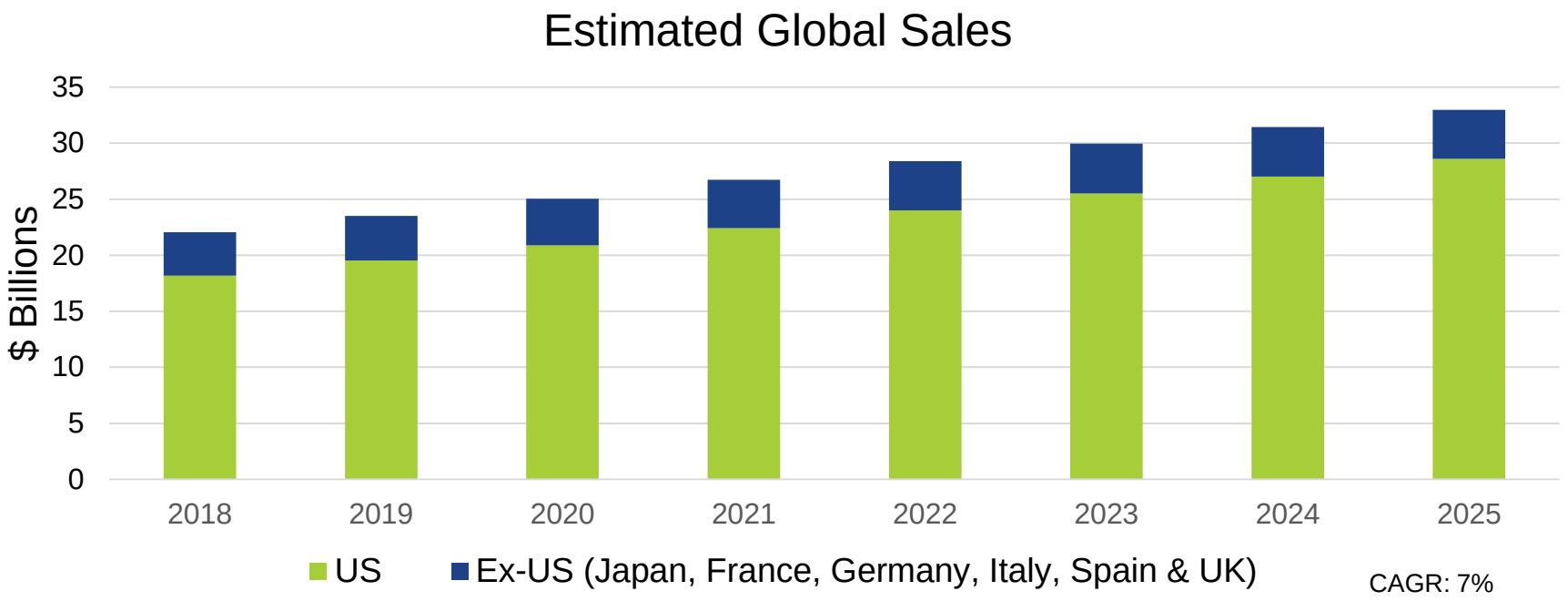
Ublituximab in Multiple Sclerosis

- A new study by the National MS Society estimates that ~1,000,000 Americans are living with MS
- Recently approved anti-CD20 (ocrelizumab) with first year sales approaching $1B
- Will compete on price and convenience
- Phase 3 ULTIMATE Trials under Special Protocol Assessment



Target Enrollment	~850
Enrollment Complete	3Q18

Multiple Sclerosis Presents a Significant Opportunity



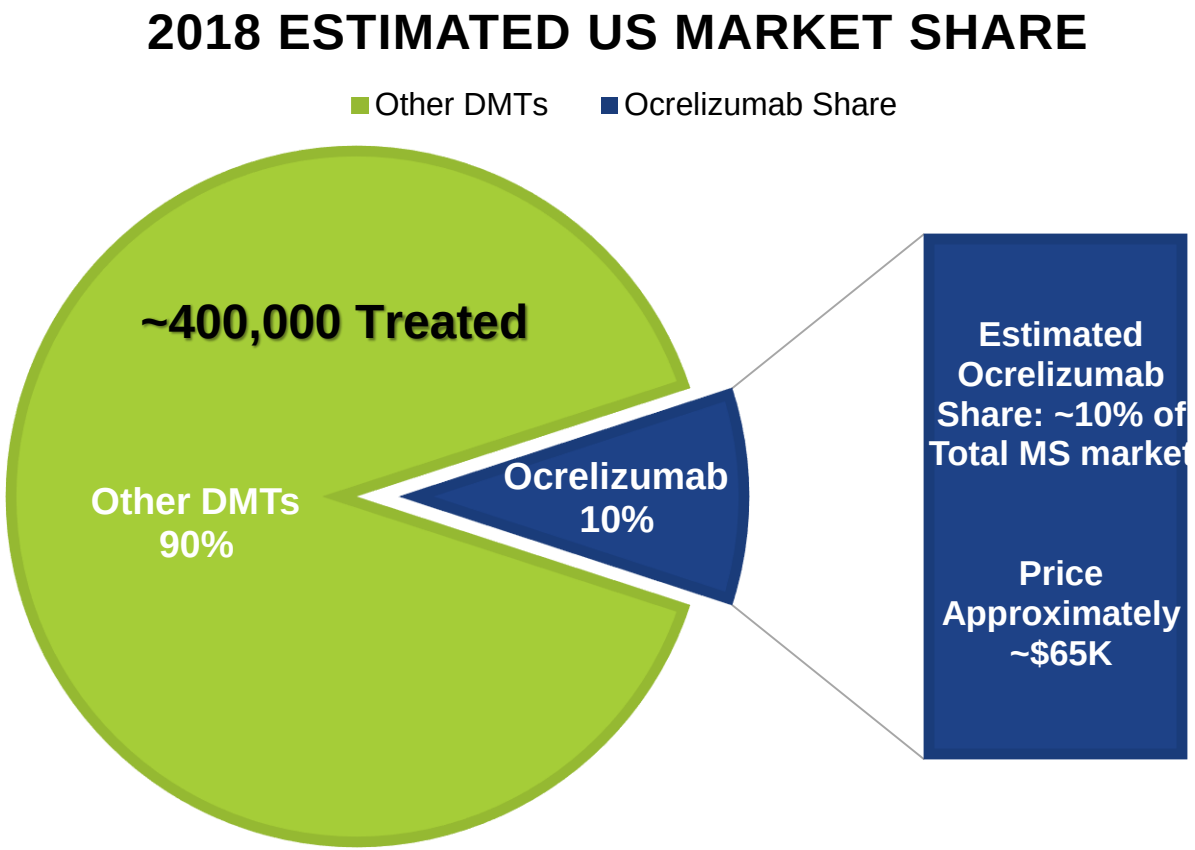
Global Prevalence = ~2.3Million

Global Market Size >$30Billion by 2025

Source: Datamonitor 2018 MS Report
Prevalence Estimate: Nat'l MS Society

Multiple Sclerosis Treatment Paradigm

- Ocrelizumab on pace to achieve $>2 Billion in 2018 annual sales
- ~90% of current revenue coming from the United States
- Most CD20 usage in more aggressive or relapsing forms of the disease following 1st line oral therapies
- Expect CD20 mAbs usage to increase over time



Source: Datamonitor 2018; Roche 2Q Investor Update

QUESTIONS???